

# Anabolic–androgenic steroid dependence: an emerging disorder

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## ABSTRACT

**Aims** Anabolic–androgenic steroids (AAS) are widely used illicitly to gain muscle and lose body fat. Here we review the accumulating human and animal evidence showing that AAS may cause a distinct dependence syndrome, often associated with adverse psychiatric and medical effects. **Method** We present an illustrative case of AAS dependence, followed by a summary of the human and animal literature on this topic, based on publications known to us or obtained by searching the PubMed database. **Results** About 30% of AAS users appear to develop a dependence syndrome, characterized by chronic AAS use despite adverse effects on physical, psychosocial or occupational functioning. AAS dependence shares many features with classical drug dependence. For example, hamsters will self-administer AAS, even to the point of death, and both humans and animals exhibit a well-documented AAS withdrawal syndrome, mediated by neuroendocrine and cortical neurotransmitter systems. AAS dependence may particularly involve opioidergic mechanisms. However, AAS differ from classical drugs in that they produce little immediate reward of acute intoxication, but instead a delayed effect of muscle gains. Thus standard diagnostic criteria for substance dependence, usually crafted for acutely intoxicating drugs, must be adapted slightly for cumulatively acting drugs such as AAS. **Conclusions** AAS dependence is a valid diagnostic entity, and probably a growing public health problem. AAS dependence may share brain mechanisms with other forms of substance dependence, especially opioid dependence. Future studies are needed to characterize AAS dependence more clearly, identify risk factors for this syndrome and develop treatment strategies.

**Keywords** Anabolic steroids, androgens, men, performance-enhancing drugs, substance abuse, substance dependence, testosterone.

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## INTRODUCTION

The anabolic–androgenic steroids (AAS) are a family of lipophilic hormones derived from cholesterol that includes the natural male hormone, testosterone, together with numerous synthetic testosterone derivatives [1]. By ingesting supraphysiological doses of these hormones, in combination with intensive weightlifting and appropriate nutrition, AAS users can greatly increase their muscle mass, often well beyond the limits attainable by natural means [2]. For decades, elite athletes have used AAS to improve performance [3]. Today, however, most AAS users are not competitive athletes, but simply individuals who want to look leaner and more muscular [1,4–8]. As we have explained in detail else-

where [9], this much larger but less visible population of illicit AAS users began to emerge in the 1980s—a trend stimulated in part by the appearance of progressively more sophisticated underground guides on how to self-administer AAS [10–14]. Western cultural developments also probably contributed to the increased prevalence of use of AAS, as media images focused increasingly on male muscularity [15–18]. Over the last few decades, even children's action toys, such as 'GI Joe' in America and 'Action Man' in the British Commonwealth, have begun to acquire the bodies of AAS users [19]. Perhaps as a result of these trends, illicit AAS use has now grown into a widespread form of substance abuse throughout western societies, including the United States [20–22], British Commonwealth countries [23–25], Scandinavian

countries [26–28] and others [25,29–31]. Although epidemiological studies in these various countries have produced a wide range of prevalence estimates, most have reported a life-time prevalence of AAS use of at least 3% in young men, suggesting that some tens of millions of individuals world-wide have used these drugs. By contrast, AAS use in women is uncommon, as women are less likely to want to become very muscular and are also vulnerable to the masculinizing effects of AAS, such as beard growth, deepening of the voice and masculinized sexual characteristics [32–35].

AAS users generally self-administer their drugs for blocks of time, called colloquially ‘cycles’. Cycles typically last 8–16 weeks, separated by drug-free intervals lasting months or years [36,37]. Planned cycles of increasing and decreasing AAS doses (‘pyramiding’) allow users to avoid plateauing (developing tolerance), minimize withdrawal symptoms at the end of a cycle and conserve drug supplies [38]. Perhaps the most important rationale for cycles, however, is the fact that exogenous AAS administration suppresses the hypothalamic–pituitary–testicular (HPT) axis, leading to decreased endogenous testosterone production in men [39,40]. If a man uses AAS in cycles, rather than continuously, then the HPT axis can rebound during the drug-free intervals between cycles, restoring normal endogenous testosterone production.

Many individuals use only a few cycles of AAS in their careers, with a cumulative life-time exposure of less than 12 months [36,37]. Such individuals often report few, if any, adverse medical or psychological effects from AAS [41,42]. On the other hand, some individuals progress from discrete cycles of AAS into a pattern of nearly unbroken use, which may continue despite prominent adverse medical, psychological and social effects [43]. This syndrome of AAS dependence has been recognized for more than 20 years; it appears to be common and possibly increasing in prevalence, as explained below, but much in need of further study [1]. Here we attempt to summarize current knowledge on AAS dependence. We begin with an illustrative case of AAS dependence, then review the accumulating human and animal literature on this topic, compare AAS dependence with classical drug dependence and suggest avenues for future research. This review is based on publications known to us, a search of publications involving ‘anabolic steroids’ in the PubMed database and additional publications referenced in these articles.

### CASE EXAMPLE

Mr A, currently 34 years old, grew up in an upper-middle-class professional family in South Florida. He reported no major social or academic problems prior to adolescence, but by age 17 developed alcohol and nico-

tine dependence, soon followed by polysubstance dependence involving marijuana, hallucinogens, alcohol and cocaine, depending on which drugs were available. At age 19 he was admitted to a detoxification facility, and thereafter remained abstinent from ‘classical’ drugs of abuse for the next 3 years. During this period, however, he began regular weightlifting in the gym, acquired AAS-using friends, and soon began to use AAS himself, starting with cycles of 12–16 weeks in duration, separated by drug-free intervals of 4–8 weeks. Like his AAS-using friends, Mr A became focused on his muscularity and often felt that he was still not big enough, despite his objective gains. He increased his doses of AAS over the next several years, reaching a maximum weekly dose of 500 mg of injectable testosterone esters, combined with 400 mg of injected nandrolone decanoate, plus 50 mg of oral methenolone per day—a total dose equivalent to more than 20 times normal male endogenous testosterone production [44]. He gained some 25 kg of muscle over the course of the first 2 years; during this time he reported increased self-confidence and mild irritability, but no major adverse psychiatric or medical effects.

At age 22, Mr A relapsed into use of classical drugs and developed opioid and cocaine dependence, reaching doses of 300 mg of OxyContin (long-acting oxycodone) per day. He continued to take AAS intermittently during this period. He underwent three detoxification admissions for opioid dependence over the next 4 years, and stopped using all classical drugs of abuse (including alcohol) successfully by age 26. By the age of 32, he also stopped smoking cigarettes. However, he has continued to use AAS steadily from age 26 to the present. During the first part of this interval Mr A still discontinued AAS for several weeks between cycles, but since age 31 he has been taking AAS virtually without interruption. He reports that if he stops using AAS, he quickly develops prominent fatigue, loss of sex drive and depressed mood. Therefore, he maintains carefully a sufficient supply of AAS to allow uninterrupted use.

Mr A now uses lower doses of AAS than when younger, with an average weekly dose of about 400–600 mg of testosterone or equivalent. He currently displays several apparent adverse AAS effects, including bilateral gynecomastia and a recent fasting total cholesterol/high-density lipoprotein (HDL) ratio of 18.6 (normal less than 5.0). Mr A expresses concern about these effects, but is reluctant to discontinue or reduce AAS because he fears ‘losing size’. He spends several hours per day at the gym, where he has many friends, most of whom are also AAS users. He has worked as a personal trainer for some time in a local health club, then at a store selling sports supplements such as protein powders and creatine. His life remains centered around

the gym and the weightlifting culture, often to the exclusion of other social or occupational opportunities.

## HUMAN STUDIES

### Initial reports and case series, 1988–1990

Mr A's history resembles that of other cases of AAS dependence reported previously. This literature began to appear in the late 1980s, starting with individual case reports describing AAS users who took the drugs initially to gain muscle for bodybuilding, but who went on to develop depression whenever they discontinued AAS use [45–47]. Interestingly, one of these individuals exhibited symptoms resembling opiate withdrawal when challenged with naloxone, although he had no apparent history of opiate use—an observation suggesting that AAS dependence might be associated with opioid-type features [45]. In the first published case series, Brower *et al.* [48] described eight AAS users with apparent dependence; all these men met two of the DSM-III-R criteria [49] for substance dependence, summarized as 'continued substance use despite problems caused or worsened by use' and 'withdrawal symptoms'. However, users varied with regard to the other DSM-III-R substance dependence criteria, many of which were designed for acutely intoxicating drugs, and which were therefore not well suited for drugs such as AAS that produce little acute intoxication.

### Studies using DSM-III-R and DSM-IV criteria, 1991–2005

Several subsequent studies in the United States, United Kingdom and Australia ([50–54]; Table 1) have also attempted to diagnose AAS dependence using the DSM-III-R [49] or DSM-IV [55] criteria for substance dependence, despite the difficulties of adapting these criteria to a non-intoxicating drug. Of 426 AAS users across these five studies, 144 (33.8%) met DSM-IV criteria for dependence, as the study authors interpreted these criteria for the case of AAS. As in the case series above, withdrawal was the criterion met most commonly, whereas 'frequent intoxication or withdrawal symptoms when expected to function' was rare, as might be expected. A sixth study, using the Structured Clinical Interview for DSM-III-R (SCID) [56], reported dependence in 10 (14%) of 71 current or past male AAS users and one (17%) of six female AAS users ([57] and D. A. Malone, personal communication, January 2009). Finally, a seventh study, also using the SCID, reported a life-time history of AAS dependence in approximately 22 (25%) of 88 male AAS users [37]. However, these latter two studies did not specify the number of AAS users meeting each individual DSM-IV

substance dependence criterion in the manner of the studies summarized in Table 1.

It should be recognized that the above studies are naturalistic studies of AAS users recruited in the field from gymnasiums [37,50–53,57] or via the internet [54]. Like all naturalistic studies of illicit substance abusers, these studies are potentially vulnerable to various forms of bias [58,59]. For example, dependent AAS users may have been either more or less likely to agree to participate in these studies than non-dependent AAS users or AAS non-users, resulting in selection bias. Information bias may have resulted if respondents failed to disclose that they had used AAS, or failed to report adverse or undesirable outcomes associated with AAS use. Confounding variables, such as premorbid attributes of AAS users or concomitant use of other substances, may have also influenced observed associations. However, because human AAS dependence cannot, ethically, be studied prospectively under laboratory conditions, these field studies currently represent our best available evidence regarding this syndrome.

### The prevalence of AAS dependence

Collectively, the above seven studies suggest that about 30% of illicit AAS users develop dependence—although it must be remembered that this estimate might be influenced by selection bias. For example, individuals who had experimented only briefly with AAS might be under-represented in samples recruited from gymnasiums, causing the studies to overestimate the prevalence of AAS dependence. In any event, however, there is reason to suspect that the prevalence of clinically significant AAS dependence may be increasing. This impression is based on the observation that the mean age of onset of AAS dependence in the above studies appears to be in the late 20s. Therefore, adverse psychiatric and medical effects of prolonged AAS dependence would probably not surface until age 30 or later [1,9]. When it is considered that illicit AAS use did not become widespread until the 1980s, as discussed above, it follows that within the subgroup of AAS users who have developed chronic use, many are only now growing old enough to show clinically significant AAS dependence. Therefore, as new waves of recent younger AAS users reach their 30s and 40s, the prevalence of AAS dependence may continue to rise.

We can illustrate the above considerations using prevalence data on male AAS users in the United States. American surveys over the last 20 years have estimated that 3–11% of male high school students have used AAS [5,21,60–64]. We have suggested elsewhere that some of these estimates may be too high [35]—but even using the lowest figure of 3%, it would follow that over the last 20

**Table 1** Numbers of individuals meeting DSM criteria for substance dependence in five field studies of anabolic-androgenic steroid (AAS) users.

| Study  | Brower <i>et al.</i> (1991) [50] |      | Gridley & Hamrahan (1994) [53] |      | Midgley <i>et al.</i> (1999) [52] |      | Copeland <i>et al.</i> (2000) [51] |      | Perry <i>et al.</i> (2005) [54] |      | Total   |      |
|--|----------------------------------|------|--------------------------------|------|-----------------------------------|------|------------------------------------|------|---------------------------------|------|---------|------|
|  | No. <sup>a</sup>                 | %    | n                              | %    | n                                 | %    | n                                  | %    | n                               | %    | n       | %    |
| DSM-IV criteria  | 49                               |      | 21                             |      | 50                                |      | 100                                |      | 206                             |      | 426     |      |
| 1 Tolerance  | 9                                | 18.4 | 4                              | 19.0 | 7                                 | 14.0 | 12                                 | 12.0 | 56                              | 27.2 | 88      | 20.7 |
| 2 Withdrawal   | 41                               | 83.7 | 12                             | 57.1 | 17                                | 34.0 | 64                                 | 64.0 | 56                              | 27.2 | 190     | 44.6 |
| 3 Substance taken in larger amounts than intended  | 25                               | 51.0 | 8                              | 38.1 | 16                                | 32.0 | 12                                 | 12.0 | 58                              | 28.2 | 119     | 27.9 |
| 4 Desire yet unable to cut down or control use   | 8                                | 16.3 | 8                              | 38.1 | 10                                | 20.0 | 17                                 | 17.0 | 8                               | 3.9  | 51      | 12.0 |
| 5 Much time spent on substance-related activity  | 19                               | 38.8 | 14                             | 66.7 | 2                                 | 4.0  | 9                                  | 9.0  | 78                              | 37.9 | 122     | 28.6 |
| 6 Other activities replaced by substance use   | 14                               | 28.6 | 10                             | 47.6 | 2                                 | 4.0  | 29                                 | 29.0 | 21                              | 10.2 | 76      | 17.8 |
| 7 Continued use despite knowledge of problems  | 18                               | 36.7 | 10                             | 47.6 | 12                                | 24.0 | 35                                 | 35.0 | 31                              | 15.0 | 106     | 24.9 |
| Individuals meeting three or more DSM-IV criteria  | 28                               | 57.1 | 12                             | 57.1 | 13                                | 26.0 | 23                                 | 23.0 | 68                              | 33.0 | 144     | 33.8 |
| DSM-III-R criteria   |                                  |      |                                |      |                                   |      |                                    |      |                                 |      | n = 120 |      |
| 8 Intoxication or withdrawal symptoms when expected to function or when physically hazardous | 4                                | 8.2  | 0                              | 0.0  | 2                                 | 4.0  | -                                  | -    | -                               | -    | 6       | 5.0  |
| 9 Substance used to relieve or avoid withdrawal  | 2                                | 4.1  | 4                              | 19.0 | 14                                | 28.0 | -                                  | -    | -                               | -    | 20      | 16.7 |

<sup>a</sup>All samples were 100% male except that of Copeland *et al.*, which included six females, of whom two were reported to meet DSM-IV criteria for AAS dependence.

years, more than 1 million American boys initiated AAS use as teenagers. Furthermore, as the median age of onset of initial AAS use in the United States appears to be considerably older than age 19 [35,36], one must add to this figure at least another million American men in the last two decades who first initiated AAS use after the age of 19. About half of this 20-year cohort of American AAS users is still under age 30 today. If we estimated conservatively that the risk of AAS dependence among these men was only 14%—the lowest figure reported among the seven studies above—it would still follow that in the United States alone there are hundreds of thousands of still-young chronic AAS users who are only now approaching the age where they may show clinically significant AAS dependence. Chronologically, most other western countries probably lag the United States in the onset of widespread AAS use—placing them earlier on this possible curve of rising AAS dependence.

### Features of AAS dependence

Despite the substantial prevalence of AAS dependence, little is known about the features of AAS-dependent individuals. Several studies have noted that dependent users consumed significantly more AAS than non-dependent users, as measured by total dose [50], number of different AAS taken simultaneously [53], total number or length of AAS cycles [50,51,54] or cumulative duration of AAS use [53]. When demographic correlates of dependent use were assessed [50,51], however, no differences between dependent and non-dependent users were found. Two studies reported a significantly greater likelihood of either aggressive symptoms [50] or 'roid rage' [51] in dependent versus non-dependent users. However, none of the studies in Table 1 assessed life-time psychiatric disorders systematically in user groups.

One new study has recently assessed demographic variables and life-time psychiatric disorders in men with AAS dependence ( $n = 20$ ) compared to non-dependent AAS users ( $n = 42$ ) and AAS non-users ( $n = 72$ ) [8]. In this study, non-dependent AAS users exhibited virtually no significant differences from non-users on any of a wide range of demographic variables or life-time psychiatric diagnoses, whereas the dependent AAS users differed markedly from both comparison groups on a number of measures. Specifically, dependent AAS users were significantly older and more muscular than the other groups; more likely to have had a single parent by age 13; more likely to report a first-degree relative with a substance use disorder; and less well educated. Dependent AAS users also reported a much more frequent history of conduct disorder than non-dependent AAS users and a much higher life-time prevalence of non-alcohol substance dependence than either comparison group; the latter dif-

ferences were driven largely by a strikingly higher prevalence of opioid abuse and dependence—an important finding that we discuss in more detail in the following paragraphs.

### The association of AAS dependence with opioid dependence

Several reports have suggested that AAS dependence might share features with opioid dependence in humans. As early as 1989, Kashkin & Kleber hypothesized that AAS dependence might arise in part via an opioidergic mechanism, in which AAS might potentiate central endogenous opioid activity and where AAS withdrawal would lead to a decrease in this activity and a subsequent acute hyperadrenergic syndrome [65]. This hypothesized link between AAS and opioids would seem consistent with a number of human observations including (i) the 'opioid-type features' described in the case report of AAS dependence cited above [45]; (ii) the observation that AAS users seem to be particularly at risk for developing opioid abuse or dependence [66–68]; (iii) the converse finding that men with opioid dependence were more likely to report prior AAS use than men with other forms of substance dependence [69]; and (iv) a post-mortem study of Swedish AAS users, reporting that AAS appeared to reduce the threshold for heroin overdose [70].

The recent field study described above adds further evidence for a relationship between AAS and opioids [8]. Ten (50%) of the dependent AAS users in this study met DSM-IV criteria for a life-time history of opioid abuse or dependence, compared to eight (19%) non-dependent AAS users [odds ratio 6.7; (1.5, 231);  $P = 0.015$ ] and five (7%) non-users [16.3 (3.4, 78.9);  $P = 0.001$ ]. Among the various men with AAS dependence, opioid abuse or dependence began both before and after the onset of AAS use, suggesting the possibility that these forms of substance use might arise from a common diathesis.

### ANIMAL STUDIES

Animal studies offer extensive additional evidence that AAS can induce dependence, and further support a link between the actions of AAS and opioids [71]. In humans, it is difficult to separate the direct rewarding effects of AAS from the secondary rewards of increased muscularity and fitness. However, using conditioned place preference and self-administration models of reward, studies in animals have demonstrated that AAS are rewarding in a context where athletic performance is irrelevant. Rats and mice will choose to spend time in an environment where they have previously received AAS [72,73]. Hamsters will self-administer testosterone, including direct intracranial injections to the point of death, and they

develop a syndrome of high-dose testosterone intoxication with opioid-like features [74]. Moreover, this syndrome is antagonized by naltrexone, and naltrexone pretreatment will prevent testosterone self-administration [75]. Not all animal species, however, appear to self-administer AAS [76].

Animal studies also suggest that AAS modify brain opioid systems. For example, chronic nandrolone treatment in rats increased levels of endogenous opioids and their receptors in select limbic regions, including a 20-fold increase in beta-endorphin in the ventral tegmental area [77], as well as a selective reduction in dynorphin b in the nucleus accumbens [78]. Other studies in rats [79] and mice [80] have also shown that AAS may act by altering levels of opioid receptors. Actions of AAS to inhibit activity of the dynorphin/kappa opioid receptor system in the nucleus accumbens are particularly intriguing. Treatment with kappa receptor antagonists in the nucleus accumbens produces anxiolytic and antidepressant effects [81,82], similar to the effects of AAS [83]. The AAS-induced reduction in nucleus accumbens dynorphin might also facilitate dopaminergic activity [78]. However, it is notable that, unlike many other drugs of abuse, AAS do not stimulate dopamine release acutely in the nucleus accumbens [84]. This is consistent with the relatively slow time-course of AAS action, and may account for the absence of acute intoxicating effects.

Studies using the opioid antagonist naloxone have yielded variable results in AAS-treated animals. Nandrolone pretreatment enhanced withdrawal symptoms to naloxone in morphine-dependent mice [80], and

naloxone reversed testosterone-induced locomotor depression in hamsters [75]. However, naloxone produced virtually no effects in three rhesus monkeys exposed to 2 weeks of high-dose testosterone [85]. It may be that testosterone serves as a partial opioid agonist, while also acting through several other non-opioid neurotransmitter systems. Specifically, AAS display important modulatory effects on serotonin [86–92], norepinephrine [89], dopamine [93–101] and gamma-aminobutyric acid [93,100,102,103]. Animal studies have also shown that AAS modulate the effects of other drugs of abuse, such as central nervous system stimulants [104], cannabis [105] and alcohol [78,87]. Finally, androgen withdrawal is also probably a complex phenomenon that shares multiple mechanisms with other endocrine withdrawal syndromes and with withdrawal from drugs of abuse—including changes in opioid peptide systems, the mesolimbic dopaminergic system and other central pathways [106]. Although a full discussion of this literature is beyond the scope of the present paper, several recent reviews have addressed in greater detail the interactions of AAS with various neurotransmitter systems and with other drugs [71,93,101].

## AAS DEPENDENCE VERSUS ‘CLASSICAL’ DRUG DEPENDENCE

As illustrated in the above sections, AAS show both similarities and differences when compared to classical drugs of abuse (Table 2). Similarities include a characteristic

**Table 2** Similarities and differences between anabolic-androgenic steroids (AAS) and classical drugs of abuse.

| Classical drugs  | AAS  |
|--|--|
| <b>Similarities</b>  |  |
| Animals will self-administer many classical drugs  | Hamsters will self-administer AAS  |
| Withdrawal syndrome after prolonged use of many drugs  | Characteristic withdrawal syndrome after prolonged use   |
| Individuals often continue drug use despite adverse medical and psychological effects                                | Use may be continued despite adverse effects   |
| Distinct subculture surrounding use of the drug  | Well-established subculture involving the gym and body image   |
| Polydrug use common  | AAS users frequently abuse other drugs   |
| <b>Differences</b>   |  |
| Immediate reward from intoxicating effect  | No immediate intoxication, but may cause increased energy, libido, and self-confidence in addition to delayed muscular gains |
| Frequent residual adverse effects from intoxication (hangovers, sleep disruption, acute withdrawal depression, etc.) | Few immediate adverse effects  |
| Frequently impairs performance (work, driving, etc.)   | Minimal performance impairment, although irritability, aggression, and mood swings may impair social relationships           |
| Physiological tolerance develops to many drugs   | Limited evidence for physiological tolerance, although users may intentionally increase doses to increase effects            |
| Time-consuming (obtaining drug, intoxication, recovery from intoxication)  | No acute intoxication, so that drug use <i>per se</i> is rarely time-consuming   |

withdrawal syndrome, self-administration by animals as just discussed, continued use despite adverse effects, maladaptive behavioral patterns surrounding use, and comorbid abuse of other substances, as illustrated by the case of Mr A and in various reports in the literature [8,9,21,36,62,63,69,107–111]. Unlike classical drugs of abuse, however, AAS produce no immediate reward in the form of acute intoxication. In one study, for example, abstinent heroin users could readily distinguish single injections of morphine as rewarding, whereas injections of testosterone or placebo were not perceived as rewarding [112]. Although AAS may produce some feelings of euphoria and increased self-confidence, these effects are inconsistent, slow to develop, and usually immaterial in the decision to use the drugs [59]. Also, as they are not acutely intoxicating, AAS rarely compromise performance or cause acute adverse effects in the manner of drugs such as cocaine or alcohol.

This fact may explain why individuals with AAS dependence appear less likely to seek treatment than individuals with many forms of classical drug dependence, who often seek treatment because of impaired occupational function, complaints from significant others or subjective distress [113]. In addition, some data suggest that AAS users may also be reluctant to seek treatment because they distrust health professionals and doubt that such professionals have sufficient knowledge of AAS [114]. Several authors have commented on the need for professionals to become more familiar with AAS in response to these problems [113,115,116].

Given the slow time-course of AAS effects and the absence of acute intoxication, standard substance-dependence criteria, such as those of DSM-IV [55] or ICD-10 [117], do not fit AAS dependence precisely, because these criteria were generally crafted to apply primarily to acutely intoxicating drugs. However, as illustrated in a recent publication (see Table 3), the DSM-IV criteria can be adapted easily with minor modifications to capture the maladaptive features of AAS dependence [118].

It should be noted that nicotine dependence, like AAS dependence, also differs from classical drug dependence, because few users smoke tobacco for its acute intoxicating effects [119]. Indeed, in contrast to the other categories of substances, a diagnosis of nicotine intoxication does not appear in DSM-IV. Unlike nicotine dependence, however, which rarely impairs psychological or social functioning, AAS dependence is similar to other drugs of dependence in terms of its potential adverse behavioral outcomes, such as impaired interpersonal functioning and substance-induced mood disorders [43].

In the United States, most prescription drugs with abuse potential are classed as Schedules II, III or IV substances under the jurisdiction of the Drug Enforcement

**Table 3** DSM substance dependence criteria interpreted for diagnosing anabolic-androgenic steroids (AAS) dependence (from Kanayama *et al.* [118]).

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*A maladaptive pattern of anabolic-androgenic steroids (AAS) use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:*

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- 1 Tolerance, as defined by either of the following:
    - (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect; for AAS this progression to markedly larger doses may be related to dissatisfaction with the previous level of desired effect (e.g. level of muscle mass)
    - (b) markedly diminished effect with continued use of the same amount of the substance (e.g. failure to maintain the same level of lean muscle mass on a given dose of AAS)
  - 2 Withdrawal, as manifested by either of the following:
    - (a) a characteristic withdrawal syndrome, characterized for AAS by two or more of the following features: depressed mood, prominent fatigue, insomnia or hypersomnia, decreased appetite and loss of libido
    - (b) AAS are used to relieve or avoid withdrawal symptoms
  - 3 The substance is often taken in larger amounts or over a longer period than was intended. For AAS, this may be manifested by repeatedly resuming courses of AAS use after a shorter 'off' period than the individual had originally planned, or by eliminating 'off' periods entirely
  - 4 There is a persistent desire or unsuccessful efforts to cut down or control substance use. For AAS, this may be manifested by unsuccessful attempts to reduce or stop AAS use because of prominent anxiety about losing perceived muscular size
  - 5 A great deal of time is spent in activities necessary to obtain the substance, use the substance or recover from its effects. For AAS, this may be manifested by extensive time spent participating in muscle-related activities surrounding AAS use (e.g. time spent in weight training, attending to diet and supplement use and associating with other AAS users) in addition to actual time spent obtaining and administering AAS
  - 6 Important social, occupational, or recreational activities are given up or reduced because of substance use. For AAS, this may be manifested by giving up important outside activities because of an extreme preoccupation with maintaining a supraphysiological AAS-induced level of muscularity (e.g. the individual relinquishes outside activities for fear that these activities will cause him to miss workouts, violate dietary restrictions, or compromise his ability to use of AAS)
  - 7 The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance. For AAS, this includes medical problems such as gynecomastia, sexual dysfunction, hypertension, dyslipidemia and cardiomyopathy; or psychological problems such as dysphoric mood swings, severe irritability or increased aggressiveness
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Administration [120]. AAS are presently classed in Schedule III; interestingly, they represent the only class of substances in Schedules II or III that is not already recognized specifically in DSM-IV as causing a dependence syndrome [118]. Unlike most other scheduled drugs, however, AAS are available legally over the counter in many countries, and they can be ordered easily over the internet from overseas, making enforcement and interdiction difficult in countries where AAS are illegal [121].

### WHAT CAUSES AAS DEPENDENCE?

In conclusion, why do some 30% of AAS users progress from more benign casual AAS use to more chronic and malignant AAS dependence, while 70% do not? Unfortunately, as discussed above, current knowledge of human AAS dependence remains limited—indeed, arguably more limited than for any other major form of substance dependence. However, several hypotheses deserve consideration. First, the progression to AAS dependence might be catalyzed by body image disorders such as ‘muscle dysmorphia’ [17]—a form of body dysmorphic disorder, sometimes called ‘reverse anorexia nervosa’, characterized by preoccupations that one does not look sufficiently muscular [8,36,122–129]. Individuals with muscle dysmorphia may develop a maladaptive pattern of chronic AAS use because, paradoxically, they often become increasingly dissatisfied with their muscularity despite growing bigger on AAS [69,123]. However, this hypothesis remains uncertain. In an analysis of preliminary data from an ongoing study of AAS users conducted by three of the present authors (see [8]), it appears that adolescent body image disorder is associated strongly with initiation of AAS use. However, among AAS users, those who progressed to AAS dependence did not show a greater level of body image disturbance than those who did not. In other words, concerns about muscularity may bring an individual to the threshold of initially using AAS, but beyond this effect these concerns may not determine whether that individual progresses onward to AAS dependence (G. Kanayama, J. I. Hudson & H. G. Pope Jr, 2009, unpublished data).

A second possible hypothesis is that individuals who progress to AAS dependence are more biologically vulnerable to the dysphoric effects of AAS withdrawal. As noted, AAS produce a characteristic withdrawal syndrome, with both affective and hypogonadal symptoms [65,130–132]. Individuals with more severe withdrawal symptoms after initial cycles of AAS use might become increasingly prone to resume AAS to prevent these symptoms. As implied above, this possible biological vulnerability might be related to the HPT axis, to opioidergic pathways or to other neurotransmitter mechanisms.

A third possible hypothesis is suggested by the apparent overlap of AAS dependence with other forms of substance dependence and with conduct disorder. An evolving neuropsychological literature has shown that individuals with many other forms of substance dependence exhibit a cluster of cognitive attributes that might be summarized as ‘risk-taking/decision-making deficits’, such as elevated rates of delay discounting [133,134]; increased impulsivity [135–137]; and deficits in decision-making, as illustrated by performance on gambling tasks and other measures of risk-taking [135,138–140]. These deficits are also associated with antisocial or ‘psychopathic’ traits [141–144], including conduct disorder [145–147]. Conduct disorder in turn appears to be associated with AAS dependence [8], and other studies have documented criminality and so-called Cluster B personality traits, including antisocial personality, among AAS users [121,148–155]. These features may, collectively, mark an endophenotype [156] that plays a causal role in the development of substance dependence [135]. With AAS, the direction of causality might well go both ways: in individuals with these hypothesized underlying deficits, use of testosterone and presumably other AAS may shift the balance even further towards an increased sensitivity for reward and decreased sensitivity for threat or punishment, as suggested by both animal [157,158] and human studies [159,160]. No studies, to our knowledge, have assessed the possible role of such deficits in individuals with AAS dependence, but this possibility would seem to deserve further investigation.

### CONCLUSIONS

A growing literature of human and animal studies suggests that AAS dependence is a valid diagnostic entity, often associated with conduct disorder and other forms of substance abuse. The prevalence of AAS dependence may be rising, as increasing numbers of AAS users are growing old enough to have established a dependence pattern. The diagnosis of AAS dependence requires some modest adaptations of standard diagnostic criteria for substance dependence, because these criteria were designed primarily for acutely intoxicating drugs and are not suited optimally for cumulatively acting drugs such as AAS. However, as suggested above, such criteria can be adapted easily for the diagnosis of AAS dependence.

AAS dependence is arguably the only major form of world-wide substance dependence that remains largely unexplored. In particular, it remains unclear why some AAS users progress from more benign initial use to more malignant AAS dependence—and the observed overlap between AAS and opioids, in both men and animals, might possibly hold a key to this explanation. Understanding the nature and etiology of AAS dependence is a



matter of growing public health importance, as individuals with dependence probably account for the great majority of the public health problems associated with AAS, including the cardiovascular, neuroendocrine and psychiatric complications of long-term AAS exposure [9]. With an improved understanding of AAS dependence, we may be able to identify more clearly those at risk and better able to develop appropriate treatment.

#### Declarations of interest

None.

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